Design and rationale for the Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in non-responders and previously untreatable patients (SOLVE-CRT) trial

Singh, Jagmeet P ; Abraham, William T ; Auricchio, Angelo ; Delnoy, Peter Paul ; Gold, Michael ; Reddy, Vivek Y ; Sanders, Prashanthan ; Lindenfeld, JoAnn ; Rinaldi, Christopher A

Abstract: BACKGROUND Cardiac resynchronization therapy (CRT) improves outcomes, functional capacity and quality of life in patients with heart failure. Despite two decades of experience with CRT, the rate of non-response remains approximately 30%. CRT efficacy is impacted by pacing location, which is anatomically limited in conventional systems. A new wireless endocardial left ventricular (LV) pacing system allows CRT without such limitations and has shown promise in open-label studies. The purpose of this study is to evaluate its use in a patient population with poor therapeutic alternatives. METHODS The SOLVE CRT study is an international, multi-center, randomized, double-blind, sham-controlled trial of patients with Class I and IIa indications for CRT who have either failed to respond to or have been unable to receive conventional CRT. Enrollment will comprise 350 patients implanted with the wireless CRT system randomized 1:1 to therapy on (Treatment) or therapy off (Control) for the six-month period over which trial primary endpoints will be evaluated. The primary safety endpoint will measure the proportion of patients free from system- and procedure-related complications. Primary efficacy endpoints will assess absolute change in LV end-systolic volume LVESV, proportion of patients reducing LVESV by 15% and clinical composite score for Treatment versus Control patients. Primary endpoints will be evaluated on an intention-to-treat basis, though per-protocol and as-treated analysis will also be performed. CONCLUSION SOLVE-CRT will quantify the safety and effectiveness of wireless CRT in non-responders to conventional CRT and indicated patients who have been unable to receive CRT via the usual transvenous approach.

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Background Cardiac resynchronization therapy (CRT) improves outcomes, functional capacity and quality of life in patients with heart failure. Despite two decades of experience with CRT, the rate of non-response remains approximately 30%. CRT efficacy is impacted by pacing location, which is anatomically limited in conventional systems. A new wireless endocardial left ventricular (LV) pacing system allows CRT without such limitations and has shown promise in open-label studies. The purpose of this study is to evaluate its use in a patient population with poor therapeutic alternatives.

Methods The SOLVE CRT study is an international, multi-center, randomized, double-blind, sham-controlled trial of patients with Class I and IIa indications for CRT who have either failed to respond to or have been unable to receive conventional CRT. Enrollment will comprise 350 patients implanted with the wireless CRT system randomized 1:1 to therapy on (Treatment) or therapy off (Control) for the six-month period over which trial primary endpoints will be evaluated. The primary safety endpoint will measure the proportion of patients free from system- and procedure-related complications. Primary efficacy endpoints will assess absolute change in LV end-systolic volume LVESV, proportion of patients reducing LVESV by ≥15% and clinical composite score for Treatment versus Control patients. Primary endpoints will be evaluated on an intention-to-treat basis, though per-protocol and as-treated analysis will also be performed.

Conclusion SOLVE-CRT will quantify the safety and effectiveness of wireless CRT in non-responders to conventional CRT and indicated patients who have been unable to receive CRT via the usual transvenous approach. (Am Heart J 2019;217:13-22.)

Cardiac resynchronization therapy (CRT) is standard-of-care treatment for patients with mild to severe heart failure (HF), left ventricular (LV) dysfunction and interventricular electrical dyssynchrony manifested as prolonged QRS duration.[45] A significant proportion of patients are non-responsive to CRT due to the anatomical constraints of the coronary venous anatomy and/or the limitations of current technology to enable individualized LV lead placement.[1,6-8,10-12,16,18,22,24,28,32,42,44,48] A novel wireless, endocardial CRT system which overcomes such issues has recently shown promise in open-label studies of patients who failed to respond to or who could not be treated with conventional CRT.[4,38] To obtain regulatory approval in the United States and incorporation into treatment guidelines, further safety and efficacy evidence must be developed through a large-scale randomized, controlled trial. The study design of such a trial is reported herein.

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Table I. Condensed Trial Eligibility Criteria.

Inclusion:
1. Class I or IIa indication for CRT-D according to current guidelines:
   a. Class I: NYHA II-IV, EF ≤ 35%, LBBB, QRS ≥ 150 ms
   b. Class IIa: NYHA II-IV, EF ≤ 35%, LBBB, 130 ≤ QRS< 150 ms
   c. Class IIa: NYHA II-IV, EF ≤ 35%, non-LBBB, QRS ≥ 150 ms
2. Patients with a functional CRT system but despite adequate trial of Guideline-Directed Medical Therapy (GDMT) and attempts at optimal device programming have not responded for ≥6 months, with non-response defined as:
   a. EF unchanged or worsened, and
   b. Clinical status unchanged or worsened as determined by the Site Enrolment Committee, based on the totality of available clinical evidence (such as NYHA Class, exercise tolerance, QOL, and/or global assessment)

OR

Patients with a full or partial CRT system deemed 'previously untreatable' for one of the following reasons:
   a. Patients in whom CS lead implantation has failed
   b. CS lead implanted but has been programmed OFF
   c. High risk upgrades: relative contraindications to CS lead implant
3. Patient on stable GDMT, in sinus rhythm, age ≥ 18 years and provided written informed consent

Exclusion:
1. Pure RBBB
2. LVEDD ≥8 cm
3. Non-ambulatory or unstable NYHA class IV
4. Contraindication to heparin, chronic anticoagulants or antiplatelet agents
5. Triple anticoagulant patient unable tolerate peri-procedural stopping of anticoagulation therapy
6. Attempted device implant (pacemaker, ICD, CRT, LV lead) or successful co-implant within 1 month
7. Receiving lithotripsy
8. Life expectancy <12 months
9. Undergoing chronic hemodialysis
10. Stage 4 or 5 renal dysfunction evidenced by estimated GFR <30
11. Grade 4 mitral valve regurgitation
12. Implanted noncardiac electrical stimulation therapy device(s)
13. Mechanical aortic or TAVR valve(s)
14. Unstable angina, acute MI, CABG, or PTCA in the last month
15. Correctable valvular disease that is the primary cause of heart failure
16. CVA or TIA within the previous 3 months
17. Persistent/permanent atrial arrhythmia or cardioversion for atrial fibrillation in the past month
18. Moderate or severe aortic stenosis

The SOLVE-CRT study

Design and centers

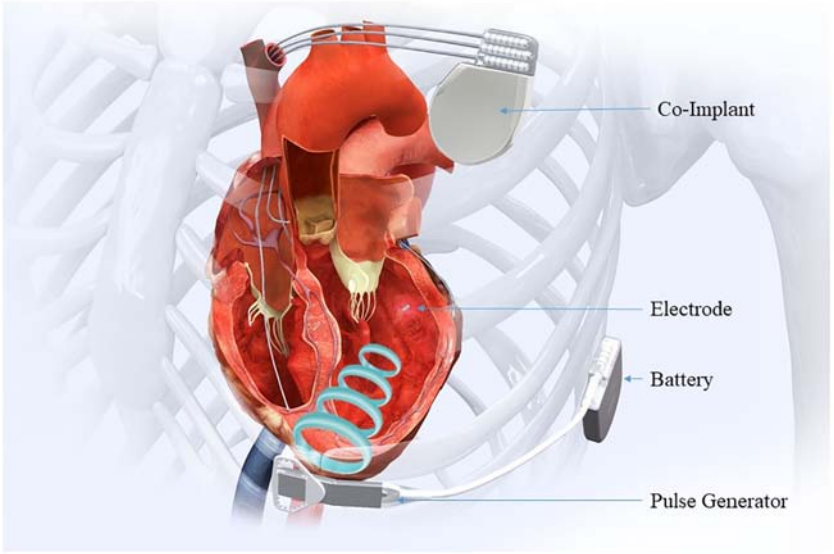
SOLVE-CRT (clinicaltrials.gov identification number NCT02922036) is a multi-center randomized, double-blind, sham-controlled evaluation of wireless CRT in 350 patients to be conducted at up to 45 centers in the United States, Europe and Australia. Up to an additional 90 patients may be enrolled as non-randomized, roll-in patients at sites that do not have experience implanting the WiSE CRT System. The trial has been designed in accordance with Good Clinical Practice standards and conforms to the Declaration of Helsinki. Regulatory approval has been obtained, as appropriate, from the competent authority and ethics committee/institutional review board applicable to each participating center. Because the system has received CE-Marking and will be used in accordance with its labeling, competent authority approval is not required within the European Union.

Patients and background therapies

Study candidates will be required to provide written informed consent before participating in any study-related procedure. Patients will be eligible for SOLVE-CRT if they have a Class I or IIa indication for CRT, based on ACC/AHA/HRS guidelines,[17] are on guideline-directed medical therapy (GDMT) and have either (1) not responded to conventional CRT for a minimum of 6 months or (2) been deemed untreatable due to aborted coronary sinus (CS) lead implantation, disabled pacing from an implanted CS lead or contraindications for CS lead implant.

Major exclusion criteria include pure right bundle branch block, excessive LV dilation, unstable/non-ambulatory NYHA Class IV heart failure, persistent or permanent atrial arrhythmias, contraindication to anticoagulation, short life expectancy, advanced chronic kidney disease, valvular disease, and recent cardiovascular/cerebrovascular events. An overview of eligibility criteria is presented in Table I. A Site Enrollment Committee at each center will be responsible for selecting potential patients for inclusion in the study based on eligibility criteria. An Eligibility Review Committee, comprised of Heart Failure specialists selected by the Steering Committee must approve any potential patients prior to enrollment in the study.

Figure 1



The wireless CRT system (WiSE-CRT, EBR Systems, Sunnyvale, California) consists of (1) a co-implanted cardiac rhythm management device, (2) a left ventricular endocardial electrode which receives ultrasound, converts it to electricity and immediately (≤5 ms) paces to administer CRT (3) a pulse generator module which emits directed ultrasound energy when right ventricular pacing is detected from the co-implant and (4) a battery.

All patients must be managed with guideline-directed medical therapy (GDMT) for HF. This is to include, but is not necessarily limited to, an aldosterone antagonist, beta-blocker and one of the following: an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker or an angiotensin receptor-neprilysin inhibitor. Doses of the foregoing medications must be stable for at least 30 days prior to enrollment with stability defined as no more than a 100% increase and no more than a 50% decrease in daily dosage relative to the dose at the beginning of the 30-day period.

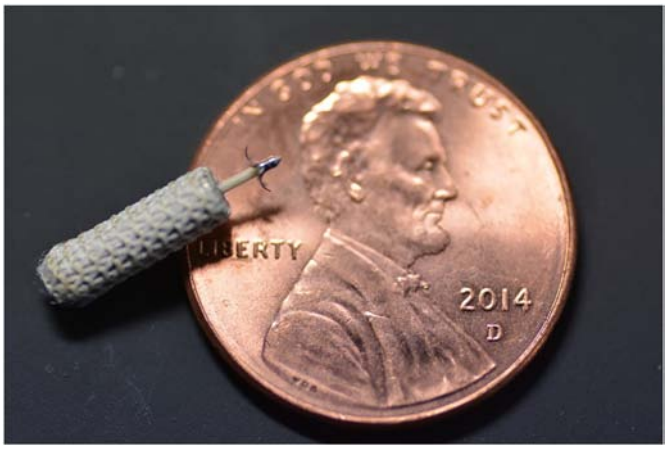
Loading of antiplatelet therapy with clopidogrel and aspirin is advised for all patients prior to implant. Intraoperatively during the implant of the Receiver Electrode, heparin is used to control clotting. Following the procedure, clopidogrel is recommended for 3 months and aspirin for the 6-month duration of primary endpoint data collection. In patients taking direct oral anticoagulants or antithrombin as background therapy, it is recommended to discontinue therapy 2–3 days before surgery (or per center practice) and restart after the implant procedure.

Wireless CRT system

The wireless CRT system (WiSE™ CRT, EBR Systems Inc., Sunnyvale, CA) has been previously described[38] and is illustrated in Figure 1. Briefly, the system is composed of an ultrasound pulse generator, a battery, an electrode with an associated delivery system and a programmer. A co-implanted cardiac rhythm management device is also required to provide right ventricular pacing for therapy and as a trigger for wireless CRT. The ultrasound pulse generator and battery module are implanted subcutaneously. The ultrasound pulse generator is typically implanted precordially in the 4th to 7th intercostal space and the battery is placed near the pulse generator along the mid-axillary line. Since an acoustic window with line-of-sight to the LV is required for efficient energy transmission, the pulse generator location is identified prior to implant using transthoracic echocardiography. Energy transfer between the pulse generator and the subsequently-implanted electrode is achieved through a two-dimensional phased array which enables the transmitter to send a narrow beam of low-intensity ultrasound directly to the electrode. The electrode converts the ultrasound that impinges on it into electricity to achieve stimulation of the endocardium.

Electrode implant is achieved through an interventional procedure under fluoroscopic guidance. A 12-F, steerable, balloon-tipped delivery sheath is introduced by femoral access and advanced into the LV in retrograde fashion through the aorta (access to the LV via an atrial transseptal approach is considered an alternative to the retrograde transaortic approach based on physician experience and the patient's risk profile (eg, peripheral vascular disease)).[39] Within the sheath is an 8-F delivery catheter pre-loaded with the electrode. The delivery sheath is positioned on selected locations of the LV

Figure 2



WiSE CRT System Electrode.

endocardial surface in the vicinity of the late-activated region and the electrode tip, which is the pacing cathode, is positioned near the end of the delivery sheath. Potential stimulation sites are evaluated for pacing capture threshold using a standard external stimulation system connected through the delivery system to the cathode. Late-activated sites suitable for pacing are localized using an electrogram measured between the electrode tip cathode and a reference on the patient. Preferred sites exhibit maximal latency from onset of the surface QRS complex to the fist large deflection observed in the local electrogram (QLV method[20,23,26,37,41]). When an optimal pacing location has been identified, the electrode is affixed to the ventricle by advancing the tip and its active fixation anchor, under fluoroscopic guidance, into the endocardium. In a recent study, an average of 3 positions were tested prior to electrode fixation and the targeted AHA segment of the heart was reached 92% of the time (an adjacent segment was reached in the remainder.)[40] The delivery system is then withdrawn. The fully-deployed electrode is a little larger than a grain of rice, displacing a volume of 0.05 cc. as seen in Figure 2. To facilitate endothelialization and minimize risk of thromboembolism, the electrode is encapsulated with a woven polyester mesh which has been observed in animal studies to become fully endothelialized within 45–60 days.[15]

Operation of the wireless CRT system is controlled by a computer-based programmer, which allows selection of three modes of operation: (1) off, (2) sensing, to assess that the system is able to accurately detect and discriminate right ventricular pacing pulses initiated by the co-implanted cardiac rhythm management system and (3) synchronous sensing and LV pacing, in which sensed right ventricular pacing pulses immediately (within approximately 5 ms) trigger transmission of ultrasound to the wireless electrode to pace the LV, thus providing CRT.

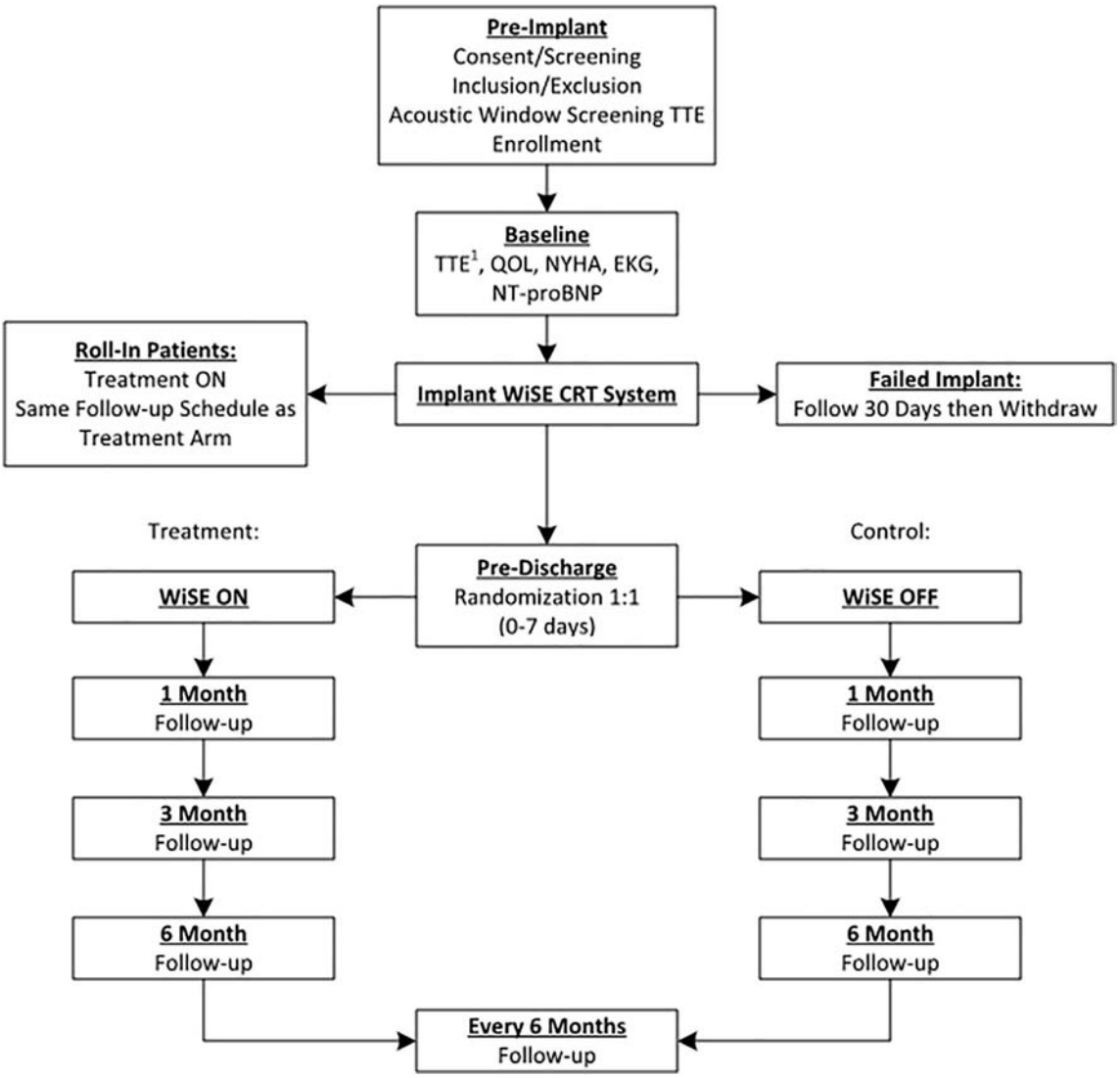
Randomization, blinding and follow-up

A block diagram of the trial flow is presented in Figure 3. Implant of the wireless CRT system will be attempted in all qualifying patients. Those successfully implanted will be randomized prior to discharge in equal proportion to the Treatment and Control groups. Wireless CRT will be activated in Treatment patients prior to discharge, whereas Control patients will begin receiving wireless CRT therapy following completion of endpoint data collection at the 6-month follow-up visit. Roll-in patients will be programmed and followed in the same manner as the Treatment group but will not be included in the endpoint analysis.

All patients will be followed at 1, 3 and 6 months subsequent to discharge for collection of randomized endpoint data, culminating in evaluation of primary trial endpoints when all patients have completed 6 months of follow-up. Non-blinded data collection will continue every 6 months thereafter until patients exit the trial. The time of trial exit is predefined as 24 months for patients outside the United States, whereas patients within US will continue to be followed until the system is approved for commercial release by FDA.

Patients and certain center staff will not be informed of randomization assignments and will be instructed to refrain from discussing the topic. Blinded center personnel will include those involved in collecting adverse events and quality of life questionnaires as well as evaluating patients during physical examination and for determining NYHA status between the time of randomization and completion of 6-month follow-up. Patients will be unblinded at the end of the 6-month follow-up visit. A log of blinded personnel will be maintained at each study site. In the event that a blinded staff member

Figure 3



SOLVE-CRT study flow diagram.

inadvertently becomes aware of a patient's randomization assignment, the loss of blinding will be documented and filed for future reference. Unblinded center personnel will participate in the randomization process in addition to echocardiographic examinations and wireless CRT system device checks during the period between discharge and 6-month follow-up completion. Aside from the aforementioned restrictions, all other aspects of trial data collection may involve blinded and/or unblinded center staff.

Endpoints

Trial primary endpoints are composed of one primary safety endpoint and three primary efficacy endpoints evaluated over the 6-month period of randomized therapy assignment. All primary endpoints must be fulfilled for the trial to be deemed successful. The primary safety endpoint is >70% rate of freedom from complications caused by a component of the wireless CRT system or procedure-related vascular events, stroke, pericardial effusion or pocket events.

The first component of the primary efficacy analysis is a comparison of change in LV end-systolic volume (LVESV) between the Treatment and Control arms. It is hypothesized that LVESV will be reduced to a greater extent in the Treatment arm. The second analysis examines a potential distribution shift in LVESV. The hypothesis is that the proportion of patients in the Treatment arm who

experience a reduction in LVESV by 15% or more will be greater than in the Control arm. The final portion of the primary efficacy evaluation compares clinical composite outcomes between the Treatment and Control arms, with a hypothesis that outcomes among Treatment patients will be superior to those of Control patients.

Outcomes assessed in the clinical composite outcomes include NYHA Class, quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), all-cause mortality, and HF-related events specified as (1) unplanned HF hospitalization, (2) emergency department visit requiring intravenous treatment with diuretics and/or inotropes to alleviate HF symptoms, (3) unplanned office visit requiring intravenous diuretic treatment to alleviate HF symptoms and (4) mechanical assist device implantation. A patient is deemed worsened if the patient dies, experiences a HF-related event, increases in NYHA class or a decrease in KCCQ score of 5 or more points from baseline. Patient status is improved if not worsened and NYHA class decreases or KCCQ score increases by 5 or more points from baseline. If not worsened or improved, the patient status is unchanged.

Two secondary efficacy endpoints evaluate the ability of the wireless CRT device to achieve and maintain capture. The first endpoint is intended to demonstrate that >80% of patients achieve an acoustic energy capture threshold of 2.9 mJ or less at the post-implant visit, representing 2:1 safety margin over the maximum transmitter output of 5.8 mJ. The second endpoint is geared toward demonstrating that >80% of patients experience a change in the acoustic energy capture threshold at 6 months of less than 3 times the value at pre-discharge, indicative of long-term capture threshold stability.

Four tertiary efficacy endpoints further assess the impact of wireless CRT on measures of HF clinical status between Treatment and Control arms over 6 months: mean change in NT-proBNP, proportion of patients with a change in LV ejection fraction >5%, mean change in intrinsic QRS duration and proportion of patients who improve by at least one NYHA Class. Additional pre-specified ancillary analyses will further explore wireless CRT device function and the impact of wireless CRT on HF clinical status.

Statistical considerations

The trial sample size of 350 patients is driven by the need to power adequately the 3 primary efficacy endpoints. In all sample size calculations, an attrition rate of 15% is assumed yielding an evaluable data set of approximately 300 patients. Change in LVESV between active CRT and sham control (non-CRT cardiac rhythm management device) has been estimated in a meta-analysis of 5 trials at 26 mL.[25] For conservative design purposes, a mean difference of 22.5 mL is assumed for SOLVE-CRT, providing 90% power at a standard deviation of 60 for a two-sample t-test at a one-sided alpha level of 0.025.

With respect to relative improvement in LVESV, previous studies indicate that 55% (range 44%–62%) of subjects achieve an improvement of at least 15%.[6,7,20,23,36,46] In the MADIT-CRT trial,[43] the percentage change in LVESV among defibrillator patients was 10.2 ± 8.9. Assuming this is a representative mean and standard deviation and that changes are normally distributed, the proportion of Control patients in SOLVE-CRT expected to exhibit a 15% improvement in LVESV is 32%. With at least a 20% difference between Treatment and Control arms of LVESV improving by at least 15%, the planned sample size would provide greater than 90% power for a one-sided, two-sample binomial test for differences in proportions at an alpha level of 0.025.

Previous trial results are likewise instructive regarding expectations for improvement in clinical composite outcome. In the MIRACLE-ICD trial,[49] 52.4% of CRT patients improved compared to 42.9% of defibrillator patients. Higher rates of CRT patient composite outcome improvement were observed in other major trials, ranging from 54–73%.[2,11,30,31,49] Based on these results, the Treatment and Control arm improvement rates are assumed to be 55% and 40%, respectively. This provides 80% power for a one-sided, two-sample binomial test for differences in proportions at an alpha level of 0.05. A higher alpha level is used for this endpoint to maintain power given the desire to achieve statistical significance for multiple primary efficacy endpoints.

A survey of previous studies was also used to establish the primary safety endpoint of system- and procedure-related complications associated with the wireless CRT device. The target event-free rate of 77% (lower confidence bound 70%) was selected by estimating the aggregate event rate from interventions similar to the wireless CRT implant procedure, including conventional CRT device implant, percutaneous coronary intervention, trans-aortic valve implantation and ablation for ventricular tachycardia. Relevant events included device dislodgement, pocket complications, vascular complications and cerebrovascular events. At the planned level of enrollment, the analysis of patients free from events included in the endpoint is powered at the 85% level with a one-sided alpha level of 0.05.

For the purposes of fulfilling trial endpoints, all analyses will be conducted on an intention-to-treat basis. Per-protocol analyses are also pre-specified in the statistical analysis plan to enable further insight into treatment effects of active versus inactive wireless CRT. In addition, an as-treated analysis will also be evaluated to mitigate effects of control or treatment patients prematurely crossing over to the other treatment group (ie, control to treatment, or treatment to control). Roll-in patients will be analyzed and reported separately from the randomized study population.

When analyzing primary and secondary efficacy endpoints, a gatekeeping approach will be applied to control the Type I error rate. Primary efficacy endpoints will be

analyzed first. If significant results are obtained, the first secondary efficacy endpoint will be evaluated and so on in a hierarchical fashion. If significance is not achieved for an endpoint, formal testing will conclude and the remaining endpoints will be summarized using descriptive statistics. No Type I error control will be applied to the tertiary endpoints.

Missing data will be addressed with multiple imputation. To understand the effect of missing data on primary endpoints, tipping point analyses will be conducted that include all possible combinations of imputed values. Such an analysis includes the best- and worst-case analyses as extremes. Primary and secondary endpoint analyses will also be performed separately for subgroups to assess consistency of results. Subgroups are defined by baseline characteristics including sex, race, age, HF severity and prior treatment history. Consistency of primary efficacy, primary safety and secondary efficacy outcomes will also be summarized by geographic region (ie, US vs. non-US). Poolability will be examined by evaluating the interaction of study site with endpoint results. Low-enrolling sites will be grouped for this purpose.

Study administration and timeline

To provide impartial guidance on design and administration of SOLVE CRT, the sponsor has chartered an Eligibility Review Committee, a Steering Committee, a Clinical Events Committee and a Data Safety and Monitoring Board. The Eligibility Review Committee will be comprised of Heart Failure Specialists who will review appropriate patient enrollment with the individual Site Enrollment Committees (comprised of an EP and an HF Specialist at each site). Inclusion/exclusion criteria will be reviewed along with the patients' GDMT optimization and stability, and patient life expectancy will be confirmed to be >12 months. The Steering Committee, with representation from and support of the sponsor, is responsible for the trial design, protocol, statistical analysis plan, publications and overall study execution. The role of the Clinical Events Committee, which is blinded to randomization assignment, is to independently adjudicate adverse events tied to trial endpoints. The Data Safety and Monitoring Board (DSMB) will review unblinded safety and efficacy data to ensure the scientific integrity of the study, safety of current and future trial participants and effectiveness of the wireless CRT device. The DSMB will also make recommendations to the sponsor regarding continuation, modification or termination of the study based on review of trial results. With the approval of the Steering Committee, the sponsor has contracted with independent core laboratories to analyze echocardiograms, 12-lead electrocardiograms and 24-hour Holter monitor recordings.

The sponsor will retain monitors to assure data accuracy and biostatisticians to independently analyze results according to the statistical analysis plan and other requests submitted by the various committees. Statistical analyses will be conducted in SAS version 9.3 or above (SAS Institute, Cary, N.C.), R version 3.2 or above (R Core Team, http://www.R-project.org) or another validated statistical software package.

The SOLVE-CRT study commenced enrollment in the first quarter of 2018. Accrual of the planned 350 randomized patients is expected to take 18 to 24 months, resulting in primary endpoint data becoming available in 2020.

Discussion

Challenges of conventional CRT

Despite two decades of clinical experience with CRT, the challenge of non-responding patients remains persistent. Approximately 30% of those implanted do not experience clinical improvement in response to treatment,[1,18,32] with estimates of the non-responding population ranging from 18% to 45% depending on the definitions used.[18] Reasons for lack of response may include patient selection,[22] myocardial scarring,[6,7] LV lead position[42,44] and device programming including optimization of CRT timing and percentage of time delivering CRT.[16,24]

Populations also exist in which CRT has not been a viable treatment. For example, CS lead implantation fails in a non-trivial percentage of patients, with failure rates of 7.6% in MIRACLE,[1] 5% in CARE-HF[12] and in COMPANION[10] 13% for CRT-P and 9% for CRT-D. Such failures are often the result of constraints within the coronary venous anatomy restricting access to an appropriate LV epicardial pacing site. A further 8–10%[11,28] of otherwise eligible patients do not benefit from CRT as a result of (1) CS leads abandoned due to issues such as excessive pacing thresholds, phrenic nerve stimulation or dislodgement and (2) contraindications to CS lead implantation stemming from safety concerns including co-morbidities, venous occlusion and infections in the pulse generator pocket.

Patients indicated for, but underserved by, conventional CRT could benefit from alternative approaches. While use of epicardial electrodes placed via thoracotomy has been an option since the advent of CRT, this option is infrequently used due to a variety of factors including procedure invasiveness, lead durability and patient acceptance. Trans-septal and trans-atrial approaches have also been proposed for LV lead placement but have not been widely adopted due to other issues including the need for long-term anticoagulation.[9,33] Thus, there remains a significant unmet need and an opportunity for new techniques.

Importance of pacing site selection

In evaluating options, the question of optimal pacing location should be considered. The late-activated region of the LV has long been recognized as an important target of resynchronization.[13] Short- and long-term outcomes in

patients paced from the site of latest LV activation are improved compared to patients with other pacing sites using a variety of indicators including echocardiography and hemodynamics.[5,20,50] Recent data further suggest that patient-specific tailoring of LV pacing to the site of latest activation may improve CRT clinical response.[23,26] Interest has also been directed toward endocardial LV pacing due to its more physiologic depolarization and repolarization characteristics.[19,47] Endocardial pacing eliminates the inverted pattern of depolarization and repolarization imposed by epicardial pacing as well as the attendant increased dispersion of refractoriness which may elevate risk of proarrhythmia. In practice, acute and chronic human studies have shown endocardial LV pacing may improve hemodynamics and clinical outcomes relative to epicardial pacing, albeit with additional risk of stroke and TIA associated with leads resident in the LV.[9,33]

The WiSE CRT system

Consequently, a clear unmet need exists for the wireless CRT system under evaluation in SOLVE-CRT. The small size and pro-endothelialization coating of the electrode substantially reduce the risk of thromboembolic events. In addition, there are no significant anatomical barriers to deploying the wireless LV pacing electrode in the preferred locations. While the system does require a suitable acoustic window for energy transfer, this posed a challenge in <8% of patients enrolled in the most recent trial (clinicaltrials.gov identification number NCT01905670).[38] The open-label evaluation enrolled 35 patients who previously failed to respond to or had constraints preventing delivery of conventional CRT. Implantation was successful in 34 patients while 33 met the study primary endpoint of LV pacing at 1 month, with 31 of 33 patients showing LV pacing at 6 months. System safety was favorable and meaningfully improved compared to a previous version[4] due to the addition of an atraumatic balloon tip to the endocardial delivery sheath. Nonetheless, 3 patients experienced perioperative device- or procedure-related adverse events including one case of ventricular fibrillation during LV catheterization. One acute cerebrovascular accident also occurred in a patient with atrial fibrillation due to noncompliance with anticoagulation therapy with no residual neurological deficit on recovery. Six months of wireless CRT resulted in significant improvements LV ejection fraction, end-diastolic volume (LVEDV), end-systolic volume (LVESV), intrinsic QRS duration, NYHA Class, and clinical composite score in the SELECT LV study population. Importantly, benefits were observed in the majority of patients despite previous failure or inaccessibility of CRT.

Subsequent to the SELECT LV study, additional patients have been enrolled as a part of an ongoing Registry (clinicaltrials.gov identification number: NCT02610673), which aims to document patient outcomes upon implant, at 6 months and annually out to 5 years. The most recent report from this study aimed to evaluate one key advantage of the small wireless electrode used in the WiSE CRT System, the ability to target delivery within the LV. The study showed that, regardless of the technique used, using targeting methods to determine electrode placement allowed the investigators to achieve results superior to those seen in SELECT LV.[40]

Thus, while safety and performance data accrued to date are promising and have been sufficient to secure CE-Marking, a solid evidence basis is required for wireless CRT to achieve its full potential. The endpoints of SOLVE-CRT are intended to compellingly address this need.

SOLVE CRT study endpoint rationale

The primary safety endpoint focuses on complications related to the system and procedures associated with wireless CRT. By highlighting these adverse events, the safety profile associated with using the system will be made clear. Fulfillment of the pre-specified event-free rate by the system will demonstrate safety parity with comparable procedures to provide assurance that the risk level is appropriate in light of anticipated benefits.

The first two primary efficacy endpoints examine the Treatment versus Control reduction in LVESV and the difference in proportion of patients reducing LVESV by 15% or more. Reduction in LVESV is a useful marker of improved LV structure and function, as its value is reduced both by LV remodeling and by increased LV ejection. More importantly, reductions in LVESV versus Control have been shown in previous HF trials to predict improved patient outcomes.[25,43] Concurrent use of the two endpoints highlights the effects of wireless CRT from a population as well as an individual patient perspective. The third efficacy endpoint is a well-known composite of important clinical outcomes, including objective endpoints as well as clinician and patient perceptions. Inclusion of this endpoint provides further assurance that structural/functional improvement is linked with improved outcome. The secondary efficacy endpoints, which measure pacing threshold and threshold stability, are important assessments of long-term feasibility of wireless CRT pacing in the population as this will characterize the ability to establish and maintain capture. Finally, tertiary efficacy endpoints examine other variables frequently assessed in HF with reduced ejection fraction to provide meaningful comparisons with other therapies.

Sham control

As a randomized, double-blinded, sham-controlled trial, SOLVE-CRT will minimize the impact of placebo and Hawthorne effects as well as other sources of bias inherent in open-label studies. Although many of the elements comprising the endpoints are objective in nature, recent studies in HF have provided a reminder that even objective variables may be susceptible to the

effects of trial participation and a belief that a new therapy is in effect. Vagus nerve stimulation for HF provides a case in point: despite promising results from a single-arm feasibility trial which included significant LV remodeling[14] and other improved biomarkers, a randomized, controlled outcomes trial failed to achieve its primary endpoint despite expanding enrollment based on interim analysis.[21] In contrast, landmark trials of CRT[1,10,12,34,49] have shown improvement in remodeling, functional capacity, survival and other important markers for patients with active CRT compared to patients with cardiac rhythm management devices not delivering CRT (ie, sham controls).

Limitations

The current embodiment of the WiSE CRT System has several limitations that may affect the SOLVE CRT Study as well as clinical use. To begin with, the device requires the presence and activity of a co-implant device. While all SOLVE CRT patients would have a co-implant by nature of their treatment history, this limitation may affect the extensibility of these results. In addition, the device requires the availability of an adequate acoustic window for ultrasound transmission. While this is easily assessed and yields only an 8% failure rate, the limitation does affect how many patients may be treated. Lastly, there are significant energy losses incurred by the transmission of power through ultrasound. Though current devices have an average lifespan of 4.5 years and batteries may be replaced without pulse generator and electrode replacement, this limitation may lead to additional surgeries for the patient.

Conclusion

In conclusion the purpose of the SOLVE CRT study is to evaluate the short and long term safety and efficacy of the wireless endocardial LV pacing using the WiSE CRT System. The SOLVE CRT study will provide a thorough and robust evaluation of this approach. A positive outcome would demonstrate clinically meaningful improvements in Heart Failure may be delivered with an acceptable safety profile by the WiSE CRT System. This outcome would therefore enable a historically challenging patient population to receive effective therapy where none exists today.

Disclosure Statement

Dr. Singh has consulted for Biotronik, Boston Scientific Corp, Medtronic Inc, Abbott Inc, Microport Inc, EBR Inc, Respicardia Inc, Impulse Dynamics, BackBeat Inc and Toray Inc.

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